## Remarks

### I. Status of the Claims

Claims 1-8, 17-23 and 32-35 are pending. Claim 28 has been canceled. Claims 1 and 17 have been amended to recite that the dosage form is a delayed burst release dosage form, that the compressed core is in the form of a tablet or capsule, to further define the molecular weight of the water soluble polymer, to further define the pharmaceutical agent and to recite that the overcoated shell portion provides for a delayed release of the active ingredient form the dosage form such that release of the active ingredient is delayed for a predetermined time after ingestion and wherein after said predetermined time said active agent is promptly released. Support can be found in the Specification at least at page 5, lines 10-20; page 6, lines 12-15; page 8, lines 13-15; page 11, lines 6-7; and page 23, lines 16-20. Support for new claims 32, 33, 34 and 35 can be found in the specification at least at Example 3 and Figures 1 and 2. Support for new claims 36 and 37 can be found in the specification at least at page 17, lines 28-30, page 18, lines 8-10 and lines 19-21. No new matter has been introduced by this Amendment.

### II. Rejection Under 35 U.S.C. § 103 – Claims 1, 2, 6-8, 17, 18, 22 and 23

The Examiner rejects claims 1, 2, 6-8, 17, 18, 22 and 23 under 35 U.S.C. 103 as being unpatentable over published PCT application WO 99/20745 ("Choi") in view of U.S. Patent No. 5,922,352 ("Chen et al.") and further in view of U.S. Patent No. 4,992,277 ("Sangekar et al."). Applicants respectfully traverse this rejection.

The present invention relates to a delayed burst release dosage form comprising a compressed core in the form of a tablet or capsule and an overcoated shell portion. According to claim 1, the overcoated shell portion comprises a composition comprising 40 to 95 weight percent of a high molecular weight, water soluble polymer having a weight average molecular weight of from about 140,000 to about 1,150,000 and a cloud point from about 20 to about 90° C, 5 to 25 weight percent carrageenan, and 0.5 to 5 weight percent gellan gum. The overcoated shell portion recited in claim 17 comprises a composition comprising 40 to 95 weight percent of a high molecular weight, water soluble polymer

having a weight average molecular weight of from about 140,000 to about 1,150,000 and a cloud point from about 20 to about 90° C, 5 to 40 weight percent of one or more carrageenans, and 0.5 to 30 weight percent lubricant. The core of the claimed invention comprises a pharmaceutical active ingredient selected from analgesics, anti-inflammatory agents, antiarthritics, anesthetics, antihistamines, antitussives, antibiotics, anti-infective agents, antivirals, anticoagulants, antidepressants, antidiabetic agents, antiemetics, antiflatulents, antifungals, antispasmodics, appetite suppressants, bronchodilators, cardiovascular agents, central nervous system agents, central nervous system stimulants, decongestants, oral contraceptives, diuretics, expectorants, gastrointestinal agents, migraine preparations, motion sickness products, mucolytics, muscle relaxants, osteoporosis preparations, polydimethylsiloxanes, respiratory agents, sleep-aids, urinary tract agents and mixtures thereof. The overcoated shell portion provides for a delayed release of the active ingredient from the dosage form such that release of the active ingredient is delayed for a predetermined time after ingestion and wherein after said predetermined time said active agent is promptly released.

Choi relates to an enteric coated granule prepared by coating a lactic acid bacteria seed with a water-miscible coating material and then, if desired, subjecting the first coated product to a second coating with a controlled-release coating material. Included among the laundry list of suitable first coating materials is hydroxypropylmethylcellulose, carrageenan and gellan gum. However, Choi specifically teaches that sodium alginate is preferred because its aqueous solution is neutral and is much more advantageous for the stability of lactic acid bacteria. Included among the laundry list of suitable controlled-released coating materials is hydroxypropylmethyl cellulose and gellan gum. Again the preferred coating materials are outside those presently claimed and specifically are selected from the group consisting of corn protein extract, hydroxypropylmethylcellulose phthalate, and shellac. Indeed, none of the Examples of Choi use hydroxypropylmethylcellulose, gellan gum or carrageenen, much less a combination of all three as a coating material. Accordingly, Choi fails to teach or suggest the specific overcoating composition comprising 40 to 95 weight percent of a high molecular water soluble polymer having a weigh average molecular weight from about 140,000 to about 1,150,000 and a cloud point from about 20 to about 90° C, 5 to 25 weight percent carrageenan, and 0.5 to 5 weight percent gellan gum. Nor is there any teaching or suggestion

that such a composition would provide for a delayed release of the active ingredient from the dosage form such that release of the active ingredient is delayed for a predetermined time after ingestion and wherein after the predetermined time the active agent is promptly released as now recited by the present claims.

The Examiner argues that because Choi list hydroxypropylmethylcellulose, gellan gum and carrageenan as suitable coating materials, it would be "obvious to try the polymers listed in Choi et al as a person with ordinary skill has good reason to pursue known options within his or her technical grasp." Applicants note however, that the specific combination of coating ingredients in the specified amounts recited by the present claims is much more than a predictable use of known ingredients. As discussed on page 2, line 30 to page 3, line 11, Applicants have discovered that a composition comprising a combination of a high molecular weight, water soluble polymer having a cloud point from about 20 to about 90° C and one or more carrageenans, in certain embodiments with gellan gum and in other embodiments with both gellan gum and a lubricant, may be used as a component of a dosage form, for example as the shell of a dosage form containing active ingredient in an underlying core. The high molecular weight, water soluble polymer and the carrageenan can be dispersed in water, along with other ingredients, at a temperature above the cloud point of the high molecular weight water soluble polymer, leaving the high molecular weight, water soluble polymer undissolved and the viscosity of the dispersion manageable. The dispersion flows easily, and sets quickly and strongly at a relatively high temperature due to the presence of the carrageenan. Cores containing active ingredient can advantageously be coated with this composition, preferably by molding, to prepare dosage forms that provide a burst release of the active ingredient. In contrast, Choi specifically teach that the coating ingredients are dissolved prior to coating the lactic acid bacteria containing seed and should be conducted at low temperatures. See Choi page 1, second full paragraph; page 5, first paragraph; page 7, second full paragraph; and Examples 1-9. Further, as discussed above, there is absolutely no teaching or suggestion that the specific combination of specific coating ingredients would provide a delayed burst release dosage form. Accordingly, Choi fails to teach or suggest a delayed burst release dosage form as recited by the present claims.

Further, Choi is specifically limited to granules of lactic acid bacteria containing seeds. There is no teaching or suggestion of the pharmaceutical active ingredient now recited by the

present claims. There is also no teaching or suggestion of a compressed core, much less a compressed core in the form of a capsule or tablet. In contrast, Choi relates to a lactic acid bacteria containing seed which is coated using a granulator. Accordingly, for all these reasons, Choi simply fails to render the present claims obvious.

The Examiner recognizes that Choi does not specifically teach a coating made from a high molecular weight water soluble polymer, carrageenan and gellan gum; a compressed core; or the inclusion of a lubricant, glycerol monostearate. The Examiner relies upon Chen et al. to cure these deficiencies.

Chen et al. relates to a once a day tablet containing a calcium channel blocker tablet that is provided with a core having delayed release properties which contains an enteric coated calcium channel blocker compound. The Examiner argues that because Chen et al. teach the inclusion lubricants such as glycerol monostearate to the granulation for the core and that hydroxypropylmethyl cellulose is a pharmaceutically acceptable polymer which forms a hydrogel, it would have been obvious to include both into the Choi enteric coated granule of lactic acid bacteria.

Applicants respectfully disagree. Chen et al. fails to cure the deficiencies of Choi discussed above. There is no teaching or suggestion of the specific overcoated shell portion composition recited in claim 1 or claim 17, much less, any teaching that the combination of the high molecular weight, water soluble polymer, the carrageenan and gellan gum would provide a delayed release of the active ingredient from the dosage form such that release of the active ingredient is delayed for a predetermined time after ingestion and wherein after the predetermined time the active agent is promptly released. Nor is there any teaching or suggestion that the Choi granules should be compressed to form a tablet or capsule. Accordingly, Chen et al., taken alone or in combination with Choi et al. fails to render the present claims obvious.

The Examiner also relies upon Sangekar et al. as teaching the cloud point limitation recited by the present claims. However, Sangekar et al. relates to an immediate relea\se diltiazem tablet. As the Examiner is well aware, an immediate release tablet is different from an enteric coated granule. As discussed by Choi, because of the coating, the lactic acid bacteria can survive under human gastric circumstance and the granule then can be disintegrated rapidly in the intestine. This is quite different from an immediate release

formulation, which releases the active ingredient immediately. Accordingly, one of ordinary skill in the art would not look to the disclosure of Snagekar et al. to modify the coating taught by Choi. Further, even if one of ordinary skill in the art were somehow motivated to use a hydroxypropylmethylcellolose having the recited cloud point they would not arrive at Applicants claimed invention. There is no teaching or suggestion of a delayed burst release dosage form comprising a compressed core in the form of a tablet or capsule or of the specific overcoated shell composition recited by the present claims or that such a coating would provide for a delayed release of the active ingredient from the dosage form such that release of the active ingredient is delayed for a predetermined time after ingestion and wherein after the predetermined time the active agent is promptly released. Accordingly, Choi, Chen et al. and Sangekar et al., taken alone or in any combination, fail to render the present claims obvious and the rejection should be withdrawn.

## III. Rejection Under 35 U.S.C. § 103 – Claims 4, 5, 20 and 21

The Examiner rejects claims 4, 5, 20 and 21 under 35 U.S.C. 103 as being unpatentable over Choi in view of Chen and Sangekar et al. and further in view of U.S. Patent No. 5,756,123 ("Yamamoto et al."). Applicants respectfully traverse this rejection.

The Examiner relies upon Yamamoto et al. as teaching the inclusion of inorganic cations. However, Yamamoto et al. fail to remedy the deficiencies of Choi, Chen et al. and Sangekar et al. discussed above. Accordingly, for at least those reasons this rejection should be withdrawn.

## IV. New Claims 32-35

New claims 32 and 34 relate to a dosage form according to claims 1 and 17 respectively, wherein said predetermined time is at least four hours, wherein less than 20% of the pharmaceutical active ingredient is released prior to said predetermined time. Claims 33 and 35 relate to a dosage form according to claims 32 and 34, respectively, wherein the pH of the media in which the pharmaceutical active ingredient is released is 6.8. None of the references relied upon by the Examiner, taken alone or in any combination, teach or suggest such a dosage form.

## V. New Claims 36 and 37

New claims 36 and 37 relate to a dosage form according to claim 1 and 17 respectively, wherein said core and said shell are prepared by thermal setting molding or thermal cycle molding. As discussed above, Choi teach coating the lactic acid bacteria using a granulator and specifically teaches that the "temperature of granule is maintained from 25 to 55°C throughout the whole procedures since lactic acid bacteria may be destroyed at the temperature exceeding 55°C." Accordingly, there is no teaching or suggestion of a core and shell dosage form prepared by thermal setting or thermal cycle molding and new claims 34 and 35 are patentable over the references of record.

## VI. Conclusion

For the foregoing reasons, Applicants believe that the present application is now clearly in condition for allowance. Accordingly, favorable reconsideration of the amended claims in light of the above remarks and an early Notice of Allowance are courteously solicited. If the Examiner has any comments or suggestions that could place this application in even better form, the Examiner is requested to telephone the undersigned Attorney at the below-listed number.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 10-0750/MCP5007USCIP1/WEM.

Respectfully submitted,

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